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Non-pharmacological interventions for management of fatigue among children with cancer: systematic review of existing practices and their effectiveness

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Title: Non-pharmacological interventions for management of fatigue among children with cancer: systematic review of existing practices and their effectiveness

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ABSTRACT

Objectives: Fatigue is common among children living with cancer, particularly in advance stages. Little is known about the effectiveness of non-pharmacological approaches to manage this complex and distressing symptom among children. Thus, the present paper aim to critically examine the effectiveness and setting for non-pharmacological interventions to manage fatigue among children with cancer.

Methods: Six electronic databases were screened first in February 2013 and at second instance in March 2015. They include PsycINFO, Medline, EMBASE, CINAHL, Scopus, and Cochrane library. All databases were systematically searched for literature on fatigue and cancer, limited to children (as age group) and English language.

Results: 1498 articles were identified, of which six were reviewed. Three types of interventions for managing fatigue were identified including: (i) complementary and alternative medicine (healing touch/massage therapy); (ii) exercise-based interventions; (iii) nursing-based interventions. Most interventions were delivered during active treatment and in hospital settings where parents were involved to optimise participation. Despite fatigue scores being lower among intervention groups, no study findings were observed as being statistically significant.

Conclusion: Fatigue is common among children treated for, and living with, cancer. The most appropriate setting to deliver non-pharmacological interventions to manage fatigue appears to be in hospital. However, in absence of any strong evidence professionals need to be cautious about existing non-pharmacological interventions. Future research must adopt more rigorous research designs that are adequately powered using validated measures to identify potential benefits. In addition, researchers may wish to test psychosocial interventions shown to be of benefit in adults.

Key words: Cancer, fatigue, children, non-pharmacological, complementary therapy

INTRODUCTION

Fatigue is one of the most common symptoms patients with cancer experience irrespective of age.^{1,2} A Cochrane review reported that prevalence of fatigue during cancer treatment ranged from 25% to 99%.³⁻⁵ However, compared to adult population, little is known about fatigue among children⁶⁻⁸. Two studies indicate it ranges from 35.6%⁹ to 93%¹⁰. A retrospective study conducted among parents reported that 96% of children experienced fatigue in last month of their life of whom nearly 50% experienced severe distress.⁶ A number of reasons for this absence of evidence may be present. First, children with cancer undergo aggressive treatment focusing on curing disease where adverse side effects including fatigue tend to get less attention because they are not adequately recognized by patients themselves, or unintentionally ignored by clinicians.¹¹ Second, inability of children to vocalise their experiences of fatigue may also be present. Despite this paucity of evidence fatigue can be particularly distressing among children with advanced cancer^{7, 12} and can dramatically compromises their quality of life.¹³⁻¹⁵ In light of current epidemiology, cancer-related fatigue among children needs special focus for its holistic management and adding quality to their life.

Fatigue has been defined in a number of ways including a ‘physical condition’ (weakness, exhaustion, decreased performance), ‘mental state’ (impaired cognition, unstable emotions) or a combination of both.^{1,6} The ‘objective performance’ (declining abilities) and ‘subjective experience’ (patient’s perception of fatigue) are other ways to define fatigue.¹⁶ One of the most cited definitions developed by the National Comprehensive Cancer Network (NCCN)¹⁷ views fatigue as “a distressing, persistent, subjective sense of physical/emotional and/or cognitive tiredness or exhaustion related to cancer and cancer treatment, that is not proportional to recent activity or that interferes with usual functioning”.

In past two decades, attention has been focused on experiences of children living with cancer. However, research published to guide practitioners in its management is not sufficient.^{14, 18} This is because the management of fatigue is challenged by the patho-physiology of this symptom occurring alongside many inter-related symptoms including pain, cachexia, anorexia, depression and anxiety either due to cancer itself or its treatment.^{1, 16,12, 17}

The management of fatigue includes pharmacological and non-pharmacological interventions. A small but growing literature suggests that non-pharmacological interventions may offer potential to relieve the physical and psychological distress associated with fatigue among children.¹⁹ However, these studies require scrutiny to appraise their claims that they offer benefits including an improvement in quality of life. This review therefore critically appraises the effectiveness of non-pharmacological interventions for management of cancer related fatigue among children.

METHODS

Selection criteria

Since the non-pharmacological management of fatigue for children with cancer is relatively new this review was not limited to one specific intervention. Therefore for the purposes of this review non-pharmacological interventions included cognitive behaviour therapy, imagery, relaxation, psycho-education, group therapy, psychotherapy, counselling, music therapy, massage, exercise, yoga, and play therapy. (Complete selection process is presented as figure 1).

We conducted an electronic search of the databases (via Ovid SP) comprising PsycINFO, Medline, CINAHL, EMBASE, Scopus and Cochrane using a broader search strategy to identify the maximum available studies on the subject. Our broad search terms for this review included 'cancer' and 'fatigue' which were searched as keywords in title, abstract, subject headings and mapped to free text. In addition, Mesh terms for cancer i.e. Neoplasm was exploded and combined, using 'or' with cancer. Similarly, 'fatigue' was exploded to yield maximum results. Finally, all search results for cancer AND fatigue was limited to children and English language. We devised a more focused search strategy for EMBASE as large number of studies was generated with broader strategy. Hence, a number of specific interventions (like cognitive therapy, behavioural therapy, counselling, psychotherapy, education, exercise, play, music, yoga, group therapy, family therapy, etc) were searched as subject headings whereas the groups of interventions like (cognitive behaviour therapy, psychosocial, non-pharmacological) were searched as free text. All the search options were then combined with 'OR' to search through Cancer AND fatigue (with limits of age and English language). Search strategy for Scopus and Cochrane was tailored to the nature of database. We purposefully kept the search strategy open to all types of research designs without any restrictions to publication year and/or database life in order to retrieve maximum literature. We conducted database search twice, first in February 2013 which was repeated in March 2015 using the same search strategy in order to include all those studies that might have been uploaded over a period of two years.

(Sample of database search strategy presented in box I).

Box 1 :DATA BASE WISE SEARCH STRATEGY

Database: PsycINFO<1806 to February Week 4 2013>

Search Strategy: (Dated: 25/2/13)

-
- 1 exp Neoplasm/ (30590)
 - 2 cancer.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (35095)
 - 3 fatigue.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (17218)
 - 4 exp Fatigue/ (5474)
 - 5 3 or 4 (17218)
 - 6 1 or 2 (40355)
 - 7 5 and 6 (1256)
 - 8 limit 7 to (English language and (100 childhood <birth to age 12 yrs> or 120 neonatal <birth to age 1 mo> or 140 infancy <age 2 to 23 mo> or 160 preschool age <age 2 to 5 yrs> or 180 school age <age 6 to 12 yrs> or 200 adolescence <age 13 to 17 yrs>)) (68)

Database: PsycINFO<1806 to March Week 4 2015>

Search Strategy (Dated:23/3/2015)

-
- 1 exp Neoplasms/ (37143)
 - 2 cancer.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (43022)
 - 3 exp Fatigue/ (6536)
 - 4 fatigue.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (20199)
 - 5 1 or 2 (49438)
 - 6 3 or 4 (20199)
 - 7 5 and 6 (1691)
 - 8 limit 7 to (English language and (100 childhood <birth to age 12 yrs> or 120 neonatal <birth to age 1 mo> or 140 infancy <2 to 23 mo> or 160 preschool age <age 2 to 5 yrs> or 180 school age <age 6 to 12 yrs> or 200 adolescence <age 13 to 17 yrs>)) (101)

Data extraction

We identified a total of 1498 studies from all the databases. We subsequently selected 152 studies on the basis of their title and then filtered them for duplicates that resulted in 58 potential eligible studies. We then screened the abstracts during which 39 publications were removed since they did not represent empirical studies or specifically focus on cancer and children. Finally, 19 studies were reviewed on the basis of meeting eligibility criteria and following inclusion criteria: (1) specifically focused on cancer and children between 0-18 years; (2) research studies (pilot/clinical-trial/quasi-experimental/); and (3) full text availability. During this process, 13 studies were excluded since they were not focused on children or fatigue was not the primary concern of the intervention. This resulted in a total of six studies to be included in this review.

Data was extracted using a standard data extraction form that included information like year of study, objectives, study design, settings, sample, measures, analytic procedures, and results facilitating transparency in data analysis. A brief review of the selected six studies is presented in table 1. Data extraction was supplemented by reviewers' critical remarks about each research included in this review as presented in table 2. Both reviewers (TB and JK) developed and then refined the structured format for data extraction.

Quality assessment and grading evidence

We used a self-developed quality assessment form to facilitate the appraisal of the reviewed studies. The selected papers were then scrutinised using standardized criteria including abstract, objectives, sample size calculation using statistical power, recruitment and retention rate, random allocation, length of intervention, use of valid outcome measures, analytic procedures and the presentation of results (table 3).

In order to ensure rigour and transparency in data extraction and quality assessment, TB first extracted the data from selected papers. JK then assessed a 30% random sample of papers to check accuracy of the data extraction and quality assessment process. We differed at few instances in relation to the reporting of the studies (specifically on study design and the reviewer's comments sections), and at six instances in relation to the quality assessment process (specifically focusing on adequacy of sample size, treatment and statistical methods). Consensus was reached after discussion.

TABLE 1: SUMMARY OF REVIEWED STUDIES

First author & year	Objectives of the study & setting	Type of study	Sample size and withdrawal	Intervention & outcomes measures	Analytic procedures	Results and comments
Wong, J ²⁰ (2013)	To determine the feasibility of healing touch in paediatric patients and its impact on treatment related symptoms Setting: In-patient/clinic, (single hospital) Place: Honolulu, USA	RCT Random generator used to allocate participants Treatment group: Healing touch (HT), 200 sessions Control group: Reading/ play activities, 30 sessions	Total: 9 (3- 18 years old) receiving chemotherapy Intervention group: 6 Control group: 3 Withdrawal: 3 all from treatment group Final sample: intervention group:3 Control group:3 Recruitment rate: 60% Retention rate: 66.6%	Once a day session for 2 months, Fatigue:(My fatigue meter), Pain:(Wong Baker) Distress:(My distress thermometer) Pre and post assessment in both arms	Wilcoxon's 2 sample test to compare differences in pre & post intervention scores in both arms	HT group showed significant decrease in pain, fatigue and distress scores, but statistical significant differences only present for pain and distress Demonstrated feasibility of providing HT to paediatric oncology patients in in-patient setting
Post-White, J ¹⁵ (2009)	To determine feasibility of massage therapy in reducing cancer related symptoms among children Setting: In-patient, two different hospitals, Place: Minnesota, USA	RCT (pilot study) – crossover design, Experimental group: Massage therapy (MT), Control group: Quiet time (QT), included activities of participants' choice like, reading, play, video, talk & rest	Parent-child dyad, Children between 1-18 years of age, received 2 cycle of chemotherapy Recruitment rate: 50% Retention rate: 68% 13 children to Massage therapy first (intervention), 12 children to Quiet time first (control)	4 weekly sessions of massage by a trained therapist, first to the parent followed by patient Pre & post session assessment of pain, anxiety, nausea, vital signs like: heart rate, respiratory rate, blood pressure, Fatigue was measured at session 1 & 4 and at each follow up, Child reported Fatigue measurement: Child Fatigue scale , Parent's reported fatigue: Lansky Play Performance Scale, Structured joint interview with parent and child at the end of the study	Wilcoxon's matched pairs signed rank test to compare between and within condition, Area under the curve (AUC) for pre & post test intervention Intent-to-treat analysis, comparative content analysis	Although the scores for measures that examined heart rate, respiratory rate, pain, anxiety were significantly lower in post test, there were no statistically significant changes in fatigue scores. Children found it difficult to conceptualize the meaning of fatigue
Hinds, P.S. ²¹ (2006)	To determine the feasibility of enhanced-activity intervention among children and assess its fatigue & sleep outcomes Setting: In-patient, two sites/hospitals, Place: Texas, USA	RCT (pilot study) computer generated random assignment and matching on the basis of diagnosis for both the arms Intervention group: Pedalling stationary bicycle for 30 minutes twice a day for 2-4 days of hospitalization, Control group: standard care	29 participants between 7-18 years, either AML or solid tumour, undergoing chemotherapy, Recruitment rate: 96.6% Retention rate: 100%	Actigraph to monitor sleep, Fatigue scale: child version for 7-12 years old, adolescence version for 13-18 years, parent version and staff version, Daily sleep diary for parent's perception of child's fatigue	Intent-to treat analysis used, ANOVA (intervention, stratified for cancer type and study location) T-test, Wilcoxon two sample test (when normality assumption not valid even after transformation)	Feasibility of the intervention was reported, adolescences had higher fatigue scores in both the arms than children, No significant difference in fatigue scores in two study arms or over time (F=0.01, p=0.91) Greater sleep efficiency in intervention arm than in control arm (F=4.17, p=0.053) Parent's perception of their children's' fatigue was higher than those of the

						children
Takken, T ²² (2009)	To develop 12-week long exercise programme, examine its feasibility and assess its impact in managing symptoms among ALL survivors Setting: Community based, subjects taken from single hospital, Place: Netherlands	Quasi-experimental (before and after with single group) 45 minutes exercise session twice a week at home following instruction from the video	4 children with ALL aged 6-18 years at least 6 months post-chemotherapy Recruitment rate: 56.25% Retention rate: 44.4%	Anthropometric measures were used to record BMI, muscles strength, functional mobility & heart rate. CIS -20 for fatigue assessment	Descriptive statistics, Wilcoxon signed rank test	Frequency of the training was considered to be too much for the children, High number of drop-outs reflected difficulties in retaining children and parents for on-going participation in the programme, Although intervention was found to be feasible, no statistically significant difference between pre & post intervention scores were identified
Yeh, ChaoHsi ng ¹¹ (2011)	To examine the feasibility of home based aerobic exercise on reducing fatigue in children with ALL Setting: Single hospital setting, Place: Taiwan	Quasi-experimental (pilot study) Intervention group: 12 (30 minutes home based aerobic exercise session for 3 days a week for 6 consecutive weeks) Control group: 10 (routine care)	22 children with ALL 6 weeks post chemotherapy, Matched by age & sex (av. Age 12 years) Recruitment rate: 80% Retention rate: 91.6%	Self reported measures: PedsQL multidimensional Fatigue scale, Physical activity log, Children's OMNI walk/run scale for child's perceived exertion during exercise, Stage of change exercise behaviour for participant's intention to practice home-based exercise Timing of measurement: Pre-test (before intervention), once weekly, post-test (completion of intervention) and one month after the intervention ended	Descriptive statistics for demographic characteristics, ITT & PP analysis	Adherence rate: 67-83%(ITT), 80-100%(PP), Only on one of the fatigue sub-scales (general fatigue) was found to be moderately significant (p=0.06) cross the two groups. Moreover, this was only observed one month post completion and not before.
Genc. RE. ¹⁸ (2008)	To examine the impact of nursing intervention on decreasing fatigue syndrome in children Setting: in-patients setting in three hospital/clinic Place: Turkey	RCT, random assignment to two groups Intervention group: 30 children (Effective nursing intervention: educating participants about fatigue associated with chemotherapy decreasing daytime sleep time by engaging child in age appropriate activities 45-60 minutes session daily for 7 days) Control group: standard care	Parents and children aged between 7-12 years of age newly diagnosed with ALL receiving chemotherapy treatment for the first time Recruitment rate: undetectable Retention rate: 100%	Fatigue - Child Fatigue scale, Parent fatigue scale, Assessment in both the groups only after completion of intervention	Chi-square and Fisher test for analysing differences in demographic characteristics of the two groups, Student's t-test, Variance analysis to examine factors affecting fatigue score	Difference in the mean fatigue scores of two groups was statistically significant (t=5.25, p<0.00), Difference in the mean score of parent's perception of fatigue in the two groups was statistically significant (t=5.67, p<0.00), No significant correlation between fatigue score and child's demographic characteristics

Table 2: APPRAISAL OF METHODS OF REVIEWED STUDIES

Author & year	Appraisal
Wong, J ²⁰ (2013)	<ol style="list-style-type: none">1. Sample size and power calculation not conducted even though previous studies on HT available with adults;2. Very small sample, unequal & unmatched groups in two arms, not matched on age, gender and type of cancer;3. Unequal number of sessions in two arms introducing intervention bias, open to observer's & participants' bias as none blinded;4. No rationale presented for the choice of control group intervention;5. No hypotheses, No description about the instruments presented;6. Abstract unstructured;7. Two different statements regarding the length of intervention;8. Study is not conducive for repetition as demographic characteristics not presented clearly;9. Strength: child attractive name were used for intervention and control group.
Post-White, J ¹⁵ (2009)	<ol style="list-style-type: none">1. Description of instruments presented including the validity and reliability2. Age appropriate instruments used;3. No music, conversation used during massage session to control confounders;4. Involvement of parent is motivating factor for participation of child, though it carry the risk of bias in assessment;5. Structured interview session at the end of the experiment conducted by a neutral/ independent interviewer protected from observer's bias, but qualitative data was not appropriately used to substantiate the findings from quantitative analysis;6. Research design was not clearly presented;7. Instruments used with parents to assess their anxiety, mood and other outcomes were not mentioned appropriately;8. Age stratified sample would have given more meaningful analysis as developmental needs of children vary in accord to their age and does not remain static through all age groups (1-18 years);9. Sample size and power calculation was not done even though literature review presented a couple of studies on similar subject.
Hinds, P.S. ²¹ (2006)	<ol style="list-style-type: none">1. No blinding;2. Outliers removed from the analysis; could have been presented through whisker and box plot;3. Length of the intervention very short, though for practical reasons it could have not been extended;4. Statistical analysis results not presented clearly for further critical remarks5. Hypotheses were not clearly stated;6. Standard care to the control arm was not discussed, leaving difficulties for further replication;7. Short-term intervention might be responsible for insignificant results8. Strength: Sample & effect size for future study was calculated on the basis of findings: (d=0.5,n=64 per study arm) (d=0.8,n=26 per study arm)
Takken, T ²² (2009)	<ol style="list-style-type: none">1. Late follow-up period (12-36 months post chemotherapy), is long time to bring changes in child's daily routine, school & social responsibilities interfering with intervention;2. Participants were doing exercise intervention (treatment) at home without the supervision of therapist and were required to maintain diary themselves, introducing scope of participant's bias;3. Disease related confounders were controlled using homogeneous sample;4. Only abbreviated name for the fatigue scale may make a reader unsatisfactory (full name of the scale was not presented);5. Results of the Wilcoxon test not presented, only pre & post-training mean score were presented;6. Since a small sample was studied, it could have been followed prospectively at various time interval during the intervention phase to present a better

	<p>picture;</p> <p>7. Authors honestly highlighted limitations in term of community based intervention, and time periods selected for inclusion criteria</p>
Yeh, ChaoHsing ¹¹ (2011)	<p>1. Exercise sessions tailored to patient's health & physical functions;</p> <p>2. Before beginning the intervention participants and parents told about exercise benefits through the handbook which might have brought subjective bias;</p> <p>3. Standard care in the control arm was not described;</p> <p>4. Test of significance (for comparing means of two groups) and results not presented clearly;</p> <p>5. Fatigue scores for all the three subscales if presented on the single graph would have given much clear & comparative picture;</p> <p>6. Small sample size was recognized by the researchers and replication with bigger sample was recommended;</p> <p>7. Structured abstract presented.</p>
Genc. RE. ¹⁸ (2008)	<p>1. Specific hypotheses were framed;</p> <p>2. Validity of the instrument established before its use;</p> <p>3. P<0.00 seems to be unrealistic;</p> <p>4. Value of correlation and which correlation was performed – not mentioned</p> <p>5. Silent about Fisher test;</p> <p>6. T-test was used on ordinal data (without normality assumption),</p> <p>7. Base line data was not collected;</p> <p>8. Before and after design could have given much better comparative picture.</p>

TABLE 3: QUALITY GRADING OF THE REVIEWED STUDIES

Study	Criteria		Study 1 ²⁰	Study 2 ¹⁵	Study 3 ²¹	Study 4 ²²	Study 5 ¹¹	Study 6 ¹⁸
1.	Structured abstract		Yes	No	No	Yes	Yes	No
2.	Objectives defined	At the outset		Yes		Yes	Yes	Yes
		Implied in the paper	Yes		Yes			
		Unclear						
3.	Hypotheses framed	At the outset						Yes
		Implied in the paper		Yes				
		Unclear /Nil	Nil		Nil	Nil	Nil	
4.	Pre-sample size calculation based on statistical power		No	No	No	No	No	No
5.	Recruitment rate		60%	50%	96.6%	56.25%	80%	Undetectable
6.	Retention rate		67%	68%	100%	44.4%	91/6%	100%
7.	Blinding	Subjects	Nil	Yes	Nil	Nil	Nil (rather scope of subjective bias)	Nil
		Researchers	Nil	Nil	Nil	Nil	Nil	Nil
8.	Adequate sample size		No	To some extent	Yes	No, very small	To some extent	Yes
9.	Well defined treatment		No	Yes	No	Yes	Yes	Yes, (but not well structured)
10.	Random allocation		Yes	Yes	Yes	NA (single group)	No	Yes
11.	Method of random allocation described		Random number generator	Not mentioned	Computer generator number	NA	NA	No
12.	Description of dropout		Yes	Yes	NA	Yes	Yes	NA
13.	Length of intervention adequate		No	To a large extent	No	Yes	No	No
13.	Use of valid & appropriate measures		Yes	Yes	Yes	Unclear	Yes	Yes

14.	Intent to treat analysis	No	No	NA	No	Yes	Not required
15.	Presentation of statistical material (table, graph, numbers satisfactory)	Yes	Yes (to a large extent)	No	Yes	Yes(to a large extent)	No
16.	Statistical methods appropriate for data	Yes	Yes	No (t-test was used for ordinal data)	No	Yes	No (T-test used for ordinal data, p value unrealistic)
17.	Is p-value presented with result	Yes	No	Yes	No	Yes	Yes, but unrealistic
18.	Are results presented with Confidence Interval	No	No	No	No	No	No
19.	Discussion on hypotheses testing	None	None	None	None	None	None

RESULTS

In order to make database search more comprehensive, this search was first conducted in February 2013 that was repeated again in March 2015 using the same search strategy. Over a period of two years seven more new studies were identified after filtration, but six of them were review papers and only one was an interventional research, which was yet not available as full text. This suggests the field of non-pharmacological research for management of fatigue needs more interventional research in order to develop strong evidence. On the basis of intervention used in selected studies, these were grouped into three categories, viz. Complementary and alternative medicine based strategies (2 studies), exercise based (3 studies), and nursing intervention (1study).

Complementary and Alternative Medicine Based Strategies (CAM): CAM included massage therapy and healing touch therapy delivered by trained therapists. Two papers reported the use of CAM with children living with cancer.^{15, 20} One examined the impact of intervention on a group of symptoms including pain, distress and fatigue²⁰ whilst the other examined pain, nausea, anxiety, fatigue and physiological measures including heart rate, respiratory rate and blood pressure.¹⁵ In both studies the intervention was administered in hospital setting either as in-patient or in day care. In the first CAM parents were also given intervention (massage) to make their children more comfortable and achieve greater participation of children; this resulted in a better retention rate (73.9% as compared to 66.6%)¹⁵. In both studies, measures to score pain, nausea, distress, heart rate, respiratory rate and blood pressure were different in experimental and control groups however statistically significant differences were not observed for fatigue scores. This may be attributed to the enduring nature of fatigue requiring a longer term intervention to achieve results (only 4 weeks¹⁵ and 8 weeks²⁰ respectively in the CAM studies).

Exercise based intervention: Three studies examined the effectiveness and feasibility of delivering exercise-based interventions to manage fatigue among children with cancer. Exercise included aerobics, pedalling a stationary bicycle and physiotherapy practice sessions. Only one study examined the effectiveness of an exercise intervention in a hospital setting²¹ (either in-patient or day clinic), the two others were delivered in children's home.^{11, 22} Fatigue was the only subjective measure in two studies,^{11, 22} while Hinds and colleagues²¹ included a sleep-based outcome in addition to fatigue. Recruitment and retention rates were higher (96.6% and 100% respectively) when intervention was applied in a hospital setting²¹ compared to when delivered in participants' homes (56.25% & 44.4%)²² and (80% & 90.6%)¹¹ respectively, suggesting hospital-based interventions may be more successful in engaging and retaining participants. When the exercise intervention was delivered during active treatment participation was higher (100%)²¹ than when delivered post chemotherapy¹¹ and following treatment²². None of the studies identified statistically significant differences for fatigue scores post-intervention phase.

Nursing intervention: Only one study examined the effectiveness of nurse-based interventions to manage fatigue among children and was delivered in a hospital setting to in-patients during the course of their chemotherapy¹⁸. This complex intervention comprised standard nursing care in addition to educating children and parents about fatigue associated with chemotherapy, keeping the child engaged in distracting activities for example drawing, reading, music, decreasing the duration of daytime (typically afternoon) sleep time, and avoiding waking the child at night. The control group received standard nursing care. The strengths of the evaluation of this intervention include 100% retention rate and identified

statistically significant difference in mean fatigue scores between intervention and control groups ($t=5.67$, $p<0.00$). However, the evaluation of this intervention is compromised by short duration of the intervention, the non-blinding of participants, and small sample size.

DISCUSSION

We believe this is the first systematic review to appraise the evidence of effectiveness of non-pharmacological interventions to manage fatigue among children living with cancer. We specifically identify three types of interventions that included (i) complementary and alternative medicine (CAM) based strategies; (ii) exercise; and (iii) nursing-based interventions. Exercise based interventions were most common approach tested. However, we failed to identify a single research study based on psychosocial interventions that often have been used to manage fatigue among adult patients³. Whilst studies using this approach may reside in the unpublished domain or represent negative studies that have not been published but this may also be due to the absence of this approach. Future research studies using this approach deserve consideration.

We note a number of important methodological issues from conducting this review that focus on study design, and the populations studied. In most instances studies reviewed were conducted in just one site, often with relatively small samples. This has repercussions for the generalisation of the findings to other locations. We note, however, this does not technically rule out replication in delivery of the interventions elsewhere, but this would have to be done cautiously, and as part of a bigger study.

We suggest that crossover RCT designs with adequate samples that help eliminate heterogeneity between the two arms should be used to test interventions. However, only one study¹⁵ used this type of design. Adequate time is also a major consideration for studies; only a study²² ran over a period of 12 weeks, while others used much shorter terms to test their interventions. This suggests that length of the intervention may be one of the factors contributing to non-significant results. Another major limitations we identify non-blinding; in a number of studies neither the participants nor the therapist were blinded. Moreover children and parents were briefed about the potential benefits of intervention^{11, 20}. This provides enormous scope for bias. We also note inappropriate statistical analysis among studies; only one study used intent-to-treat analysis,¹¹ while two others^{15, 21} though mentioned the use of ITT but did not present clear results.

Research using massage interventions^{15, 20} studied all age groups of children, but others^{11, 18, 21, 22} focused mainly on older children. Further, fatigue scores were reported as being higher among older children²¹. This suggests that whilst interventions were focused on all children this could be considered to be a relatively heterogeneous patient group, with differing issues, needs and challenges across the age range. Therefore studies of interventions that stratify across by age may provide more accurate results in terms of identifying which ages benefit more. This area of investigation also highlights the conceptual difficulties experienced by children in comprehending the meaning of fatigue.¹⁵ This has enormous potential to affect outcomes. Unless psychometrically validated tools to examine fatigue among children²³ are used terms that imply fatigue must be used with caution. More colloquial terms, relevant to children across different ages, should be best tested using cognitive interviewing techniques prior to trials being conducted.

A combined analysis of the reviewed studies reflects that hospital based settings (IPD/clinics) are more successful in participant retention rate irrespective of nature of intervention. Future research studies that make use of home-based interventions may need to consider how they are able to maximise recruitment and retain participants for the duration of the interventions. Furthermore we identify the involvement of parents in engaging their children during the course of the interventions was paramount.^{11, 15, 18}

LIMITATIONS OF THE REVIEW

This systematic review has a number of methodological issues that limit the inferences that can be drawn from the results presented. First, we did not examine grey literature, or unpublished dissertations/thesis or conference proceedings. Second, the scope of the review was limited to English language. Both these limitations may have led to missing other studies relevant to the study question. Third, the varying design of the studies, heterogeneity of the populations combined with a relatively small sample sizes meant that we were only able to conduct a narrative review of the literature. Larger studies with similar methodologies and outcome measures would have enabled us to potentially conduct a meta-analysis of the study findings. Aligned to this limitation the heterogeneity of the study designs challenged using a standard tool to grade the quality of the studies. We therefore had to develop our own quality assessment tool.

CONCLUSION

In conclusion, based on the findings of this systematic review, non-pharmacological interventions for the management of fatigue among children are currently limited to massage therapy, exercise and nursing interventions although we are unable to conclusively say which intervention represents the most effective in managing this distressing symptom. This review also suggests that hospital-based setting is the best place for administration of non-pharmacological interventions as they produce high retention rates and maximize participation. Convincing evidence for effectiveness of any intervention is currently absent. Therefore in clinical practice current interventions need to be used with caution. In the meantime fatigue will remain a distressing symptom for children with cancer. Future studies with more rigorous research designs, conducted on a larger scale, are urgently required.

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Ethics: No study approval was obtained since the study does not involve human subjects.

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Figure 1: Flow chart representing the selection process of reviewed papers

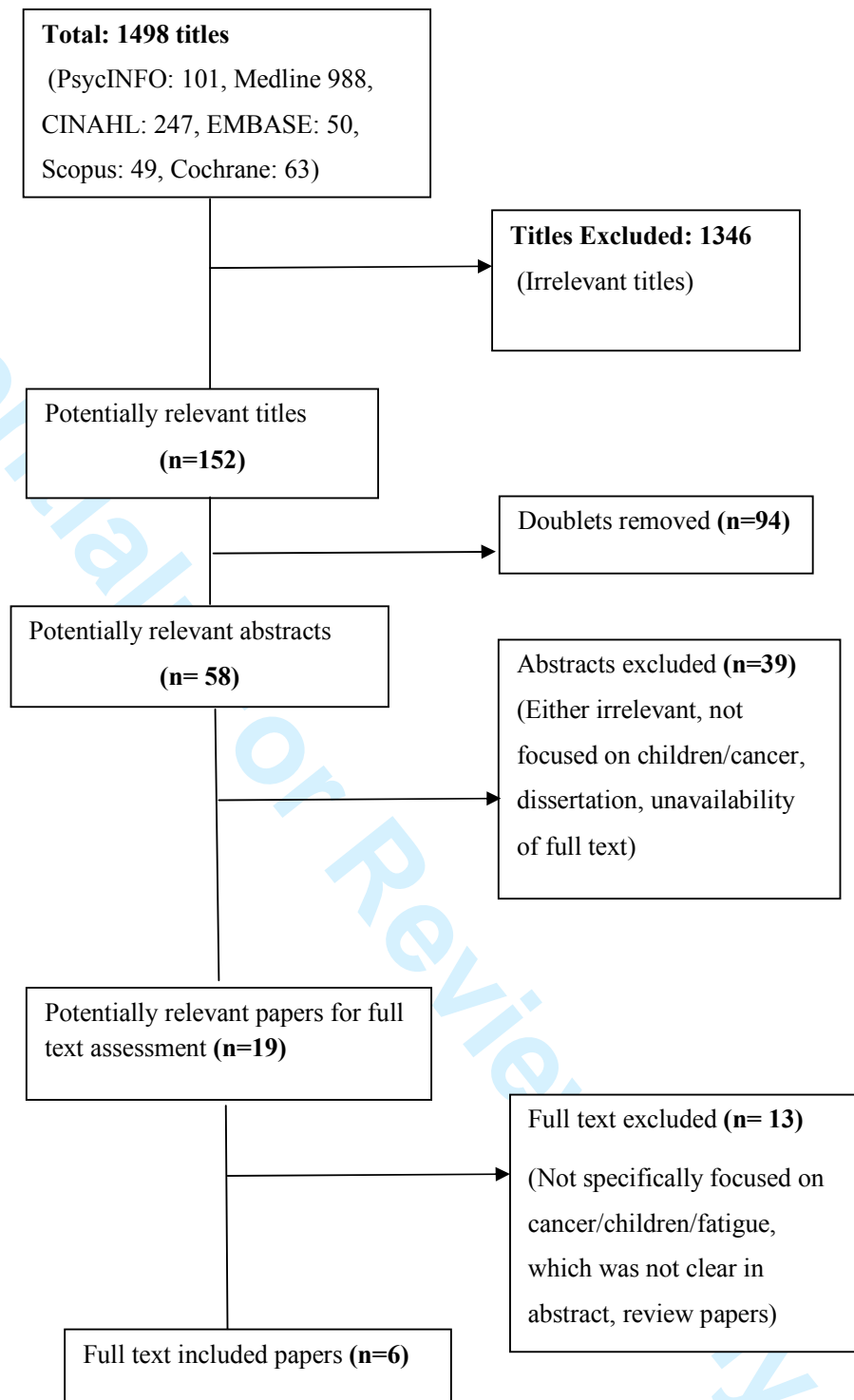


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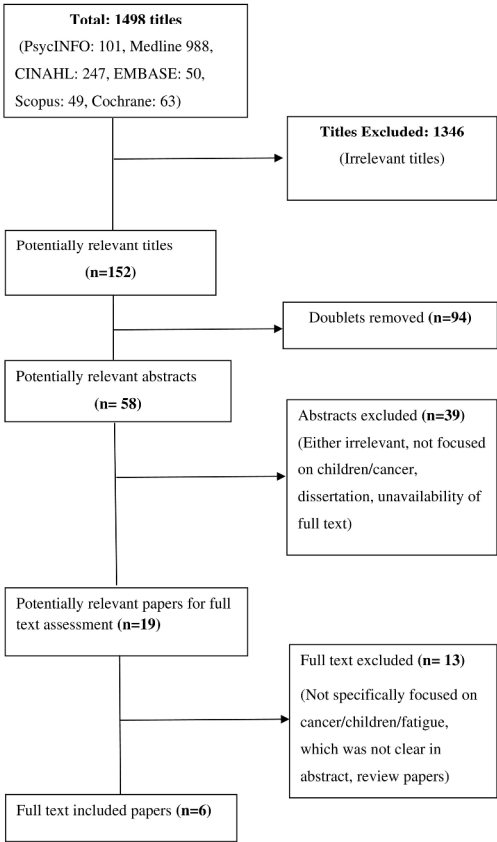


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